REMARKS

The Claim Amendments

Claims 36, 38, 48-59, and 68-69 are currently pending. Claims 36, 38, 51-59, 68, and 69 have been amended herein. Claims 48-50 have been canceled without prejudice. New claims 70-74 have been added.

With the present submission, claim 36 has been amended to recite a chemically modified nucleic acid molecule comprising a sense strand and a separate antisense strand, wherein (a) the nucleic acid molecule comprises a sense and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; (b) each strand of said nucleic acid molecule is independently 18 to 27 nucleotides in length; (c) an 18 to 27 nucleotide sequence of the antisense strand of said nucleic acid molecule is complementary to a human platelet-derived endothelial cell growth factor (ECGF1) RNA sequence comprising SEQ ID NO:225; (d) an 18 to 27 nucleotide sequence of the sense strand of said nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of said human ECGF1 RNA sequence comprising SEQ ID NO:225; (e) about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications; and (f) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

Support for claim 36 can be found in the specification as filed at, for example, pages 8, 10, 12, 13, 14, 15, 17, 26-28, and 33-38 and elsewhere in the specification.

Dependent claims 38, 51- 59, 68, and 69 have been amended, replacing the term "siRNA" in each with the term "nucleic acid" to insure proper antecedent basis.

Among these, dependent claims 51-53 and 56-58 have been further amended to replace the term "one or more" with the term "1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more." Support for these amendments can be found in the specification as filed at, for example, pages 26-28 and elsewhere.

Claim 58 has been further amended, replacing the term "comprise" with the term "are" to insure grammatical coherence, and deleting the dash after the term "2'-deoxy" to correct an inadvertent error. The scope of claim 58 has not changed as a result of these particular amendments.

Applicants have also added new claims 70-74. New claim 70 depends from claim 1, reciting a chemically modified nucleic acid molecule wherein 1, 2, or 3 of the purine nucleotides present in the sense strand are 2'-O-methyl purine nucleotides. Support for this claim can be found in the specification as filed at, for example, pages 26-28 and elsewhere.

New claim 71 likewise depends from claim 36, reciting a chemically modified nucleic acid molecule wherein the antisense strand, sense strand, or both the antisense and the sense strands include a 3'-overhang of 1-3 nucleotides. Support for this claim can be found in the specification as filed at, for example, pages 11 and 18 and elsewhere.

New claim 72 depends from claim 71, and recites a chemically modified nucleic acid molecule wherein the nucleotides of the 3'-overhang are chemically modified as specified. Support for this claim can be found in the specification as filed at, for example, pages 18, 19, and 20 and elsewhere.

New claim 73 recites a chemically modified nucleic acid molecule comprising a sense strand and a separate antisense strand, wherein (a) each strand is independently 18 to 27 nucleotides in length; (b) an 18 to 27 nucleotide sequence of the antisense strand of said nucleic acid molecule is complementary to a human platelet-derived endothelial cell growth factor (ECGF1) RNA sequence comprising SEQ ID NO:225; (c) an 18 to 27 nucleotide sequence of the sense strand of said nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of said human

ECGF1 RNA sequence comprising SEQ ID NO:225; (d) the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand; (e) one or more of the nucleotides present in the sense strand and one or more of the nucleotides present in the antisense strand are 2'-O-methyl modified nucleotides; and (f) one to ten of the pyrimidine nucleotides present in the sense strand and one to ten of the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

Support for new claim 73 can be found in the specification as filed at, for example, pages 8, 10, 12, 13, 14, 15, 17, 26-28, and 33-38 and elsewhere in the specification.

New claim 74 recites a chemically modified nucleic acid molecule, wherein: (a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; (b) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; (c) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human ECGF1 RNA sequence comprising SEQ ID NO: 225; (d) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human ECGF1 RNA sequence; (e) at least 50% of the nucleotides of each strand of said double stranded nucleic acid molecule comprise modified nucleotides having a sugar modification selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, and deoxyabasic modifications; and (f) at least one of said sugar modifications is a 2'-O-methyl modification.

Support for new claim 74 can be found in the specification as filed at, for example, pages 8, 10, 12, 13, 14, 15, 17, 26-28, and 33-38 and elsewhere in the specification.

Amendments to the claims are made without prejudice or disclaimer, and do not constitute amendments to overcome any prior art or other statutory rejections. They are fully supported by the specification as filed and thus do not introduce new matter. Additionally, these amendments are not and should not be construed as admissions regarding the patentability of the claimed subject matter. Applicants reserve the right to pursue the subject matter of the previously presented claims in this or in any other appropriate patent applications. Accordingly Applicants respectfully request the entry of the amendments presented herein.

Withdrawal of Previous Claim Rejections

35 U.S.C. § 112, second paragraph, rejections

Applicants acknowledge the withdrawal of the 35 U.S.C. § 112, second paragraph, rejections of claims 48, 51-53, 56-60, 62, and 66 as being obviated by the previously filed claim amendments.

35 U.S.C. § 103 rejections

Applicants acknowledge the withdrawal of the 35 U.S.C. § 103 rejections of claims 37, 40-46 and 60-67 as being rendered moot by the cancellation of these claims.

Priority

The Office accords the instant application a priority date of August 29, 2003, which is the filing date of the application. The Office did not accord the instant application the benefit of the priority application 60/363,124, filed March 11, 2002, because it alleges that the 60/363,124 application does not provide support for the instantly claimed invention. The Office acknowledges that provisional application 60/363,124 recites the instantly claimed target, ECGF1, as GenBank Accession Number NM_001953 (SEQ ID NO: 225). However, the Office alleges that GenBank Accession Number NM_001953 is a DNA sequence comprising thymidine nucleotides while SEQ

ID NO: 225 recited in the claims is an RNA sequence comprising uridine nucleotides. The Office therefore concludes that because the prior application discloses a DNA sequence having GenBank Accession No. NM_001953, and the instant claims recite an RNA sequence having SEQ ID NO: 225, the prior application does not provide support for the instantly claimed invention.

Applicants submit that the instant application claims priority, *inter alia*, to PCT/US03/05028, which in turn claims the benefit of provisional application 60/363,124, among other applications. Both PCT/US03/05028 and provisional application 60/363,124 teach the instantly claimed invention. PCT/US03/05028 provides support for GenBank NM_001953 (SEQ ID NO: 225) at page 458 of the specification. Provisional application 60/363,124, filed March 11, 2002, provides support for GenBank NM_001953 at page 341 of the specification.

Applicants submit that the claims as amended are drawn to chemically modified nucleic acid molecules comprising a sense strand and a separate antisense strand having the recited chemical modifications wherein the antisense strand comprises 18 to 27 nucleotides that are complementary to a platelet derived endothelial cell growth factor 1 ECGF1 RNA sequence comprising SEQ ID NO: 225. Both PCT/US03/05028 and provisional application 60/363,124, as well as other applications to which the instant application claims priority, teach the instantly claimed invention. For example, support in PCT/US03/05028 for a chemically modified double stranded nucleic acid comprising a sense strand and antisense strand, wherein the antisense strand is complementary to a ECGF1 nucleotide sequence comprising SEQ ID NO: 225 (GenBank NM_001953) is found in Table V on page 458. Support for the other claim elements in claim 1 can be found throughout the PCT/US03/05028 specification, and particularly at, for example, pages 9, 10, 11, 14, 20-22, 23, 27-31, 34-35, and 53-56. Support for the dependent claims as amended can be found in PCT/US03/05028 at, for example, pages 8, 10, 12, 14, 15, 20-23, 24-25, 37-41, and 45. Support in USSN 60/363,124 for a chemically modified double stranded nucleic acid comprising a sense strand and antisense strand, wherein the antisense strand is complementary to a ECGF1 nucleotide sequence comprising SEQ ID

NO: 225 (GenBank NM_001953) is found in Table III, on page 341. Support for the other elements of claim 1 and for the other dependent claims as amended can be found in the 60/363,124 application at, for example, pages 3, 5, 6, 7, 9-11, 12, 15-17, 18, 19, 21-22, 24, 27-31, and page 40.

With respect to the Office's allegation that GenBank NM_001953 is a DNA sequence comprising thymidine nucleotides, Applicants respectfully submit that the Office is in error. According to the Customer Service at the National Center for Biotechnology Information (NCBI), which hosts GenBank, the nucleotide base codes that are used with the GenBank International Nucleotide Sequence Database follow the IUPAC nomenclature system, which is presented below.

7.5.1 Nucleotide base codes (IUPAC)

Authority Nomenclature Committee of the International Union of Biochemistry

Reference Cornish-Bowden, A. Nucl Acid Res 13, 3021-3030 (1985)

Contact EMBL

Scope Location descriptors

Listing

Symbol	Meaning
a	a; adenine
c	c; cytosine
g	g; guanine
t	***t; thymine in DNA; uracil in RNA***
m	a or c
r	a or g
w	a or t
s	c or g
y	c or t
k	g or t
v	a or c or g; not t
h	a or c or t; not g
d	a or g or t; not c
b	c or g or t; not a
n	a or c or g or t

According to the internationally accepted IUPAC nomenclature, the 't' in a nucleotide sequence represents thymine in DNA and uracil in RNA. Thus, one skilled in the art familiar with the IUPAC nomenclature system and the GenBank database would understand that the symbol "t" is used to represent both thymine (in DNA) and uracil (in RNA). Since "t" represents both thymines and uracils, the GenBank Accession Number NM_001953 can represent both a DNA sequence comprising thymine nucleotides **and** an RNA sequence comprising uracil nucleotides.

Further, Applicants submit that NM_001953 is identified in the GenBank database as an "mRNA" sequence having 1600 nucleotides. A portion of the GenBank entry for NM_001953 is provided below.

```
LOCUS       NM_001953       1600 bp    mRNA    linear   PRI 31-OCT-2000
DEFINITION  Homo sapiens endothelial cell growth factor 1 (platelet-
derived)
            (ECGF1), mRNA.
ACCESSION   NM_001953
VERSION     NM_001953.2  GI:7669488
KEYWORDS    .
SOURCE      Homo sapiens
ORGANISM  Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
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Given that in the GenBank database, the symbol "t" is used to represent both thymines and uracils, and given that NM_001953 is identified as an mRNA sequence, one of ordinary skill in the art would have known that NM_001953 is an RNA sequence and not a DNA sequence.

For the reasons set forth herein, the disclosures of the priority documents comply with the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants submit that the instant invention is entitled to a priority date of at least March 11, 2002, the filing date of the 60/363,124 application.

Objection to the Specification

The Office objects to the amendments filed on May 19, 2006, and November 15, 2006, because they allegedly introduced new matter into the specification. Specifically, the Office alleges that the sequence listing filed with the November 15, 2006 amendment

added SEQ ID NO: 225, which represents GenBank NM_001953. The Office states that the sequence having SEQ ID NO: 225 is an RNA sequence containing uridine residues whereas GenBank Accession No. NM_001953 submitted in the originally filed application on August 29, 2003, is a DNA sequence as indicated by thymidine residues in the sequence. Thus, the Office concludes that the instant specification does not support the newly submitted RNA sequence having SEQ ID NO: 225.

Applicants respectfully submit that SEQ ID NO:225, which represents NM_001953, is not new matter. As discussed above, the symbol "t" is used in the IUPAC nomenclature system and the GenBank database to represent thymine nucleotides in DNA and uracil nucleotides in RNA. As further discussed above, Accession Number NM_001953 is identified in GenBank as an mRNA sequence and not a DNA sequence. Given that the RNA sequence of SEQ ID NO: 225 is identical to the RNA sequence of GenBank NM_001953, the nucleotide sequence of SEQ ID NO: 225 is fully supported by the instant specification as filed and thus does not constitute new matter. Applicants respectfully request withdrawal of this objection.

Claim Objection

Claim 38 was objected to under 37 CFR 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, the Office alleges that claim 38, which depends from claim 36, recites "wherein the siRNA molecule comprises one or more ribonucleotides", however, claim 36 recites a short interfering RNA molecule and therefore would have at least one ribonucleotide. Without acceding to the merits of the objection, and solely in the interest of expediting prosecution, Applicants have amended claim 36 to recite a "nucleic acid molecule", thereby obviating the objection. Applicants respectfully request withdrawal of this objection over claim 38.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Written Description

Claims 36, 38, 48-59 and 68-69 have been rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse.

The Office states that claim 36 recites "a siRNA molecule... complementary to platelet-derived endothelial cell growth factor (ECGF1) nucleotide sequence corresponding to SEQ ID NO: 225". (Office Action, page 5). Alleging that the instant specification does not define the term "corresponding," the Office looked to the plain meaning of the term and determined it to mean "[t]o be similar or equivalent in character, quantity, origin, structure, or function". (Office Action, page 5). Based on that definition, the Office contends that one skilled in the art would reasonably conclude that RNAs similar to SEQ ID NO: 225 are also within the scope of the claimed invention. (Office Action, pages 5-6). The Office argues that since one of ordinary skill would not be able to envision the genus of molecules being instantly claimed, Applicants have not described the invention in a way that one of ordinary skill in the art would recognize that Applicants had possession of the claimed genus at the time of filing.

Without acceding to the merits of the Office's rejection, and solely in the interest of expediting prosecution, Applicants have amended items b. and c. in claim 36 to recite that the antisense strand of the nucleic acid molecule is complementary to an ECGF1 RNA sequence comprising SEQ ID NO:225 and the sense strand comprises a nucleotide sequence of the ECGF1 RNA sequence comprising SEQ ID NO:225. In view of these claim amendments, this written description rejection under 35 U.S.C. § 112, first paragraph, is moot, and should be withdrawn.

New Matter

Claims 36, 38, 48-59 and 68-69 have been rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement due to the alleged addition of new matter. Applicants respectfully traverse.

The Office argues that the originally filed specification discloses the instant target ECGF1 as GenBank Accession No. NM_001953, however, the addition of SEQ ID NO: 225 (which was added to the sequence listing filed on May 19, 2006) adds new matter because SEQ ID NO: 225 is an RNA sequence and GenBank Accession Number NM_001953 is a DNA sequence. The Office therefore concludes that "the specification does not contemplate a chemically modified siRNA comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a RNA sequence corresponding to SEQ ID NO: 225". (Office Action, page 7).

Applicants respectfully disagree. The application teaches throughout the specification that the nucleic acid molecules are complementary to and target ECGF1 RNA sequences. For example, the specification teaches that:

> In one embodiment, the invention features a siNA molecule having RNAi activity against ECGF1 and/or ECGF1r **RNA** wherein the siNA molecule comprises a sequence complementary to any **RNA** having ECGF1 and/or ECGF1r encoding sequence, such as those sequence having GenBank accession Nos. shown in **Table I**." (emphasis added) Specification, page 8, lines 14-17.

Table I includes GenBank Accession No. NM_001953. Thus, the specification clearly describes nucleic acid molecules comprising nucleotides that are complementary to ECGF1 **RNA** nucleotide sequence comprising SEQ ID NO: 225.

Furthermore, as discussed previously, GenBank Accession No. NM_001953 discloses an RNA sequence, not a DNA sequence. Thus, one of ordinary skill in the art would have recognized that the RNA sequence of SEQ ID NO: 225 is the same as the RNA sequence reported in GenBank NM_001953.

For the reasons set forth above, one of ordinary skill in the art would have understood that Applicants were in possession of the invention at the time the application was filed. Therefore, the claims have adequate written description. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 54-55 and 68 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the

subject matter which Applicants regard as the invention, because the claims, which depend from claim 47, recite an "siRNA molecule" and it is unclear which siRNA the claims are referring to since claim 47 has been canceled.

Applicants submit that claim 54 has been canceled, rendering the rejection moot as to that claim. Claims 55 and 68 have been amended to depend from claim 36, thereby reciting the nucleic acid molecule of claim 36. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph, rejections.

Obviousness-Type Double Patenting Rejections

The Office has maintained the obviousness-type double patenting rejections of claims 36, 38, 48-59, and 68-69 over claims 1, 3, 14-21, 30, and 35-36 of copending Application No. 10/922,034. As proposed previously, Applicants will consider filing a terminal disclaimer upon allowance of the claims herein.

Claim Rejections - 35 U.S.C. § 103

The Office has maintained the 35 U.S.C. 103(a) rejection of claims 36, 38, 51-53, 56-59, and 68-69 as allegedly being unpatentable over Wyatt *et al.* (U.S. Patent No. 6,716,975), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Tuschl *et al.* (WO 02/44321), Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), and Cook *et al.* (U.S. Patent No. 5, 587,471). Applicants respectfully traverse the rejections.

Post-KSR Framework for Obviousness Inquiries

Subsequent to the filing of Applicants' previous responses, the Supreme Court of the United States addressed the legal standard for determining obviousness under 35 U.S.C. § 103 in *KSR International. Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007).

At the outset, reaffirming the objective standard for obviousness set forth in *Graham v. John Deere Co. of Kansas City,* (383 U.S. 1, 17-18 (1966)), the KSR Court held that the teaching-suggestion-motivation test ("the TSM test") previously devised by the Federal Circuit, if not applied in a rigid and mandatory formula, is consistent with the

Graham analysis. *KSR,* at 1731. Thus, the arguments and submissions regarding obviousness in Applicants' previous responses, which followed the TSM test framework, are still valid post *KSR*.

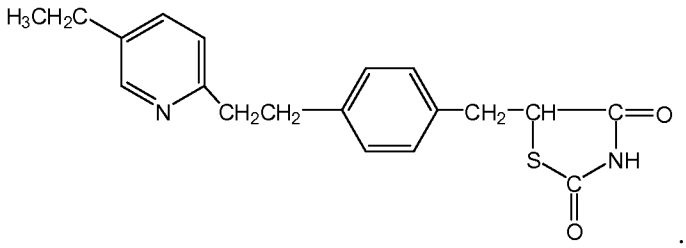
The *KSR* decision focused on how to determine obviousness when all elements of a claimed invention can be found in the prior art. Recognizing that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known," (*KSR*, at 1741), the Supreme Court emphasized three factors: (1) whether there is an "apparent reason to combine the known elements in the fashion claimed by the patent at issue," *id.* at 1740-41; (2) whether, when known elements are combined, there is predictability of yielding the claimed results; and (3) whether the prior art teaches away from modifying known elements in such a way that would lead to the claimed invention. The Court found obviousness in *KSR* because "there is a design need or market pressure to solve a problem [*i.e.,* a reason] and there are **a finite number** of **identified, predictable** solutions." *See id*, at 1732 (*emphasis added*). The *KSR* Court emphasized the importance of using teaching-away references to guard against hindsight reconstruction, stating that "[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)).

As such, teaching away is significant not only in undermining the reason(s) for making a claimed invention, but also in diminishing the predictability of whether a combination of prior art elements may be successful. As discussed below, the prior art to the instant invention does just that, not only teaching away from making the claimed invention, but also suggesting the lack of predictability.

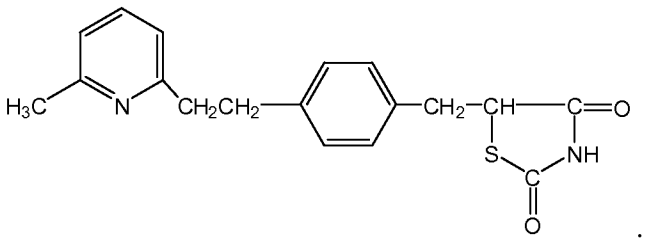
These factors have subsequently been interpreted by the Federal Circuit on several occasions. For example, applying the framework of *KSR,* the Federal Circuit held in *Pharmastem Therapeutics v. Viacell,* (83 U.S.P.Q.2d 1289, 1350 (Fed. Cir. 2007)) that it is necessary to demonstrate that the prior art provide reasons to make the particular invention and not merely general guidance before finding obviousness, and that "an invention would not be deemed obvious if all that was suggested was to explore a new

technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). Therefore, the mere fact that certain approaches can be undertaken does not constitute a legally sufficient reason to combine the known elements in an obviousness inquiry.

Takeda Chemical Industries v. Alpharma, 2007 WL1839698, *15 (Fed. Cir. June 28, 2007), further illustrates the importance of having a finite number of identified, predictable solutions for a finding of obviousness. In *Takeda*, the claim at issue was directed to the compound pioglitazone, wherein an ethyl group is attached to the 5'-position of a pyridyl ring:



The alleged infringer argued that the claim at issue was obvious over the prior art compound b, which includes a pyridyl ring with a methyl group attached at the 6'-position:



The Federal Circuit agreed with the district court's finding of nonobviousness, despite the fact that the claimed compound differs from the alleged prior art compound in merely two aspects: (1) the type of substituent (methyl in compound b vs. ethyl in the claimed compound); and (2) the location of the substituent (at the 6-position on the pyridyl ring in compound b vs. at the 5-position in the claimed compound). The Federal Circuit found that the prior art would not have first led one of ordinary skill in the art to select compound b as a lead compound for investigation, and then led that person to make two

obvious chemical changes: replacing a methyl group with an ethyl group, and "ring-walk" the ethyl group to the 5'-position, despite the fact that compound b was disclosed in a prior art reference. The Federal Circuit called attention to the fact that the reference disclosed hundreds of millions of other compounds in the same family, and exemplified 54 of those compounds, including compound b, but was silent as to which of those compounds would have the desired properties. The Federal Circuit also found it important that another reference also disclosed compound b, but did not identify it as one of the three most favorable compounds, and in fact singled it out as one having prominent undesirable side effects. On these facts, the Federal Circuit approved the district court's finding that a person of ordinary skill in the art would not have selected compound b as a lead compound.

The Federal Circuit then rejected the contention that, under *KSR*, it would have been obvious to pick compound b and modify it as claimed because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." According to the Federal Circuit, this was not a situation when there are a finite number of identified and predictable solutions to a problem. Instead, compound b "exhibited negative properties that would have directed one of ordinary skill in the art away from that compound." *Id.* at *15. Thus, the Federal Circuit concluded, "this case fails to present the type of situation contemplated by the [*KSR*] Court when it stated that an invention may be deemed obvious if it was 'obvious to try.'" *Id.*

The defendant's reliance on *Pfizer v. Apotex, Inc.,* 480 F.3d 1348 (Fed. Cir. 2007) fared no better. Contrasting *Pfizer*, where obviousness was found because the prior art teaches how to narrow the possibilities of a large family of lead compounds to a group of efficacious ones, the Federal Circuit pointed to the district court's finding of nothing in the prior art to narrow the possibilities of millions of lead compounds to compound b in *Takeda.*

The Federal Circuit went on to state that even if the prior art would have led to the selection of compound b as the lead compound, the obviousness argument failed on a second ground. The Court found nothing in the prior art to suggest making the specific

molecular modification to compound b that would lead to the claimed compounds. The Court also pointed out that studies have confirmed that several other compounds, "and one compound in particular, compound 99, that had no identified problems" in properties "differ significantly from compound b in structure." *Id.* at *18. The Court concluded that the process of modifying lead compounds was not routine at the time of the invention because of the great number of possible modifications, and because there was no way of predicting which of the modifications might bring about desired properties, especially in view of the fact that similar modifications did not always yield similar changes in properties. Therefore, there is no *prima facie* obviousness even when a general approach to a problem is known, if that general approach yields numerous choices, and the prior art does not help to predict which of those choices would be more efficacious.

Takeda therefore illustrates how a prior art reference teaching away from the claimed invention may further buttress the want of predictability. Specifically, evidence in the prior art that certain modifications produce undesirable properties should be taken as not only leading a skilled artisan away from those particular modifications, but also as suggesting the lack of predictability on how similar modifications may fare. In other words, if the prior art teaches that certain modifications sometimes but not always give rise to the desired properties, there is no way of predicting what other similar modifications may do.

The Cited References

The Office argues that one would have been motivated to substitute an siRNA for the antisense of Wyatt to modulate ECGF1 because Hammond teaches that siRNA has been shown to work more efficiently than antisense in the inhibition of gene expression. (Office Action, page 10). The Office further argues that one would have been motivated to incorporate 2'-O-methyl modifications into the siRNA molecule based on the disclosure of Tuschl because it was well known in the art at the time of the instant invention that the use of 2'-O-methyl modifications imparts duplex stability and nuclease resistance to olidonuclaotides. (Office Action, page 11). The Office further argues that Tuschl "clearly recognizes that 2'-modifications enhance the nuclease stability of siRNA molecules and therefore one would have been motivated to search for particular chemical

modifications that are tolerated by the siRNA by routine experimentation of determining the optimum number and placement of the 2'-modifications to see how well the modifications were tolerated with respect to stability and functionality of the siRNA." (Office Action, pages 11-12). Finally, the Office argues that one would have been motivated to incorporate the modifications taught by Parrish (i.e., 2'-deoxy-2'-fluoro) into the siRNA taught by Tuschl.

Applicants take the position that there is no *prima facie* case of obviousness for the present claims over Wyatt *et al.*, Hammond *et al.*, Tuschl *et al.*, Parrish *et al.*, and Cook *et al.,* because at the time of the present invention, there was no reason for those skilled in the art to apply the chemical modifications previously made on single stranded nucleic acid molecules to double stranded nucleic acid molecules. As Applicants have previously argued, at the time of the present invention, it was believed that double stranded nucleic acid molecules were substantially more stable than single stranded nucleic acid constructs, such as antisense and ribozyme oligonucleotides, and were therefore in need of little, if any modification. Thus, there was no compelling reason to make modified double stranded nucleic acid constructs, let alone the extensively modified constructs as claimed.

More importantly, Applicants submit that, even assuming a skilled artisan would find a reason to modify double stranded nucleic acid molecules using those chemical modifications that were previously applied on antisense or ribozyme molecules, potentially hundreds of thousands, if not more, prospective chemical modification patterns may be generated in a double stranded molecule that has 18 to 27 nucleotides in each strand. The cited references are either silent as to which of the modified molecules might be efficacious, or teach away from making certain of the modifications. Thus the problem faced by the instant Applicants at the time of this invention did not have a "finite number of identified, predictable solutions," and the instant claims are accordingly not *prima facie* obvious.

Specifically, the Office relies on Wyatt et al. for its alleged teaching of antisense targeted to EDG1 (ECGF1). However, the teaching in Wyatt is limited to a suggestion to use antisense oligonucleotides to target EDG1 (also known as ECGF1). Not only does Wyatt fail to contemplate using double-stranded nucleic acid molecules that are 18 to 27 nucleotides in length, it also fails to contemplate using these molecules to inhibit ECGF1, and hence at least fails to teach or suggest item a. of instant claim 36, item a of instant claim 73, or items a and b of instant claim 74. As admitted by the Office on page 10 of the Office Action, Wyatt additionally fails to teach the targeting of SEQ ID NO: 225, thus failing to teach items b. and c. of instant claim 36, items b and c of instant claim 73, or items c and d of instant claim 74. Given that Wyatt fails to teach double stranded nucleic acid molecules or siRNA molecules in any capacity, it certainly fails to teach any chemical modifications of double stranded nucleic acid molecules, much less teach or suggest the specific modification patterns recited in items d., e., and f. of instant claim 36, items d, e, and f of instant claim 73, or items e and f of instant claim 74.

The Office relies on Tuschl for teaching chemically modified siRNA, including 2'-deoxy and 2'-O-methyl modifications. Applicants disagree. Tuschl does not mention ECGF1, and thus does not contemplate using siRNA to target ECGF1. There are numerous important differences between Tuschl and the presently claimed invention. First, Applicants note that Tuschl fails to contemplate using siRNA to inhibit ECGF1, much less SEQ ID NO: 225 and hence at least fails to teach or suggest items b. and c. of instant claim 36. Furthermore, Tuschl fails to contemplate a siRNA molecule wherein the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand and therefore failing to teach item d. of claim 73. In addition, Tuschl also fails to contemplate an siRNA molecule wherein one or more of the pyrimidine nucleotides present in the sense strand and antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides, thus failing to teach item f. of instant claim 36, item f of instant claim 73, or item e of instant claim 74.

Even more significantly, Tuschl teaches that 2'-O-methyl modification abolishes RNAi activity, therefore teaching away from item e. of instant claim 36, item e of instant

claim 73, and/or items e and f of instant claim 74. Specifically, Tuschl teaches that double-stranded molecules modified beyond the 3'-terminal ribonucleotides are found to have significantly or completely diminished RNAi activity, and 2'-O-methyl substitutions are not at all tolerated. *See, e.g.,* Figure 14, pages 46, and 49-50. In particular, in "The siRNA Users Guide," Tuschl expressly states that:

> 2'-deoxy substitutions of the 2 nt 3' overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-*O*-methyl modifications, reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNAP assembly.**

See pages 49-50 (*emphasis added*). This sentiment was reaffirmed by the authors of the Tuschl reference in a published U.S. patent application No. 2004/0259247, paragraphs [0178] to [0179]). Here, the term "More extensive" in the second sentence could have only been intended to modify "2'-deoxy" and not the term "2'-O-methyl," as the first sentence does not mention "2'-O-methyl" at all. Thus, contrary to the Examiner's contention on page 11 that Tuschl only teaches that "siRNA with more extensive 2'-deoxy modifications on one or both strands or siRNA with more extensive 2'-O methyl modifications on one or both strands reduced the ability of the siRNAs to mediate RNAi", Tuschl teaches in no uncertain terms that 2'-O-methyl modifications should be entirely avoided. Therefore, Tuschl teaches away from item e. of instant claim 36, item e of instant claim 73, or items e and f of instant claim 74.

Applicants further disagree with the Examiner's multiple allegations that "one skilled in the art would have been motivated to incorporate 2'-O-methyl modifications from the disclosure in Tuschl et al. particularly given what was well known in the art at the time of the instant invention regarding the use of 2'-O-methyl modifications to impart duplex stability and nuclease resistance to oligonucleotides," (Office Action, pages 10-11), and "one of skill in the art would not interpret from those experiments in Figure 14 to mean that 2'-O-methyl would not be a useful modification of siRNA, particularly because it is well know (sic) in the art the benefits of incorporating 2'-O-methyl

modifications in any nucleic acid for increased stability and nuclease resistance." (Office Action, page 11).

As evident from the cited paragraph above, Tuschl teaches nothing more than that the 2 nucleotides at each of the 3'-overhangs may comprise 2'-deoxy modifications without losing RNAi activity. Tuschl also expressly teaches that any 2'-O-methyl modification abolishes RNAi activity. Having been taught what does not work, those skilled in the art would most certainly avoid 2'-O-methyl modifications entirely, and not pursue 2'-deoxy modifications beyond the 3'-terminal nucleotides. In fact, by teaching that 2'-deoxy modifications are only tolerated at 3'-terminal positions, Tuschl effectively teaches those skilled in the art to avoid making any internal chemical modification whatsoever.

Applicants strongly disagree with the Office's contention that Tuschl would have motivated one skilled in the art to incorporate 2'-O-methyl modifications into an siRNA molecule because it was well-known in the art that 2'-O-methyl modifications impart increased stability and nuclease resistance to antisense and ribozyme molecules. While Applicants agree with the Examiner that the antisense and ribozyme art taught that 2'-O-methyl modifications can increase the stability and nuclease resistance of antisense and ribozymes, Applicants submit that the more relevant art, **the siRNA art**, expressly teaches that **2'-O-methyl modifications should be avoided**. Regardless of whether 2'-O-methyl modifications increase the stability and nuclease resistance of siRNA, Tuschl clearly teaches that 2'-O-methyl modifications abolish RNAi activity. Importantly, this teaching has been confirmed by other researchers in the siRNA field who also expressly demonstrate that 2'-O-methyl modifications abolish RNAi activity. For example, Rana (US 2005/0020521) teaches at paragraph [0288] that:

> "2'OMe nucleotides incorporated into either the sense or antisense strand greatly diminished [target] gene silencing to ~25% or ~16%, respectively, while **double-stranded 2'OMe modified siRNAs completely abolished RNAi** (FIG. 10B and Table I, rows 12-14). These results suggest that the methyl group, as a bulky group, may severely limit the interactions between siRNAs, target mRNAs and the RNAi machinery required for successfully mediating RNAi." (emphasis added).

At paragraph [0320], Rana, who had at least the same level of skills as those ordinarily skilled in the art, concluded that "the inhibitory RNAi effects seen with the bulky 2'OMe modification, which was also shown previously with Drosophila (Elbashir et al., 2001), did demonstrate that there were steric constraints on the types of 2' modifications that would be amenable for inducing RNAi." Rana clearly showed that, due to differences in the structure and mechanism of siRNA (e.g., as compared to single stranded antisense and ribozymes which do not involve RNAi machinery), 2'-O-methyl modifications render the siRNA molecule nonfunctional. Thus, Rana confirmed the teachings of Tuschl and others (Elbashir), which clearly demonstrate that 2'-O-methyl modification abolishes RNAi activity and therefore should be avoided in siRNA molecules.

By insisting that one would have been motivated to pursue 2'-O-methyl modifications in siRNA despite the clear teachings that 2'-O-methyl modifications destroy RNAi activity, the Office chooses to selectively apply the antisense and ribozyme art while disregarding the more relevant siRNA art that teaches away from using 2'-O-methyl modifications. In doing so, the Office disregards the requisite standards for determining obviousness.

The Office relies on Parrish for teaching modifications of long dsRNA molecules, including 2'-deoxy-2'-fluoro modifications. Specifically, the Examiner alleges that "the modifications taught by Parrish et al provide stability to a dsRNA that are subsequently involved in RNAi and therefore one skilled in the art would have been motivated to incorporate said modifications into the siRNA taught by Tuschl et al." (Office Action, page 12). Applicants strongly traverse and respectfully submit that a more exact reading of Parrish would indicate it to be an unsuitable reference on which to base an obviousness rejection.

At the outset, Parrish does not teach or suggest the claim limitation that "each strand of said nucleic acid molecule is independently 18 to 27 nucleotides in length," (*e.g.,* as recited in items a., b., and c. of instant claim 36, items a, b, and c of instant claim

73, or items b, c, and d of instant claim 74, because it only teaches chemically modified long (about 742 nts) RNAs. *See* Parrish, at page 1081, left column, in the text accompanying Figure 5 ("2-fluorouracil, 2'-aminouracil, 2'-deoxythymidine, and 2'-deoxy-cytidine were incorporated **into individual strands of the 742 nt unc-22A segments** using T3 and T7 polymerases (Experimental Procedures)" (*emphasis added*)).

Further, contrary to the Office's allegation, Parrish does not teach any of the chemical modifications of the instantly claimed nucleic acid molecules. Specifically, Parrish fails to teach the claim limitation that "the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand" or the claim limitation that "one or more of the nucleotides present in the sense strand and one or more of the nucleotides present in the antisense strand are 2'-O-methyl modified nucleotides" (*e.g.,* as recited in items d. and e. of instant claim 36, item e of instant claim 73, or items e and f of instant claim 74).

Moreover, Parrish fails to teach the claim limitation that "one to ten of the pyrimidine nucleotides present in the sense strand and one to ten of the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides." (*e.g.,* as recited in item f. of instant claim 36, item f of instant claim 73, or item e of instant claim 74). To the contrary, Parrish describes 2'-deoxy-2'-fluoro uridine modifications but not 2'-deoxy-2'-fluoro cytidine modifications. Indeed, Parrish expressly describes that 2'-deoxy modification of cytidine is not tolerated. *See* Parrish, at page 1081, right column ("Modification of cytidine to deoxycytidine … on either the sense or the antisense strand of the trigger was sufficient to produce a substantial decrease in interference activity."). Taught by Parrish that cytidines should not be subject to 2'-deoxy modification if interference activity is desired, those skilled in the art would most certainly avoid 2'-deoxy-2'-fluoro cytidine modifications for fear of substantially impaired interference activity. Therefore, Parrish cannot be relied upon for teaching or suggesting the use of 2'-deoxy-2-fluoro pyrimidine modifications, as recited in item f. of instant claim 36, item f of instant claim 73, or item e of instant claim 74,

because such modifications encompass **both** 2'-deoxy-2'-fluoro uridine and 2'-deoxy-2'-fluoro cytidine substitutions.

Moreover, Parrish describes 2'-deoxy-2'-fluoro modification of uridine in either the sense strand or the antisense strand, but **never simultaneously in both strands,** as was first taught by Applicants and as is presently recited in, for example, item f. of instant claim 36, item f of instant claim 73, or item e of instant claim 74. *See, e.g.,* Parrish, at page 1081, left column, Figure 5B (describing that interference activities of unc-22 were retained with a 2-uracil → 2'-fluorouracil in the sense strand, and unmodified RNA antisense strand; or with an unmodified RNA sense strand and a modified uracil → 2'-fluoro uracil antisense strand).

The Office relies on Hammond et al. for its general teaching of dsRNA and RNAi. But as discussed previously, Hammond merely discusses dsRNA and RNAi generally. Hammond does not teach or suggest targeting ECGF1. Hammond does not teach or suggest an siRNA molecule, much less a chemically modified siRNA molecule. In fact, Hammond does not mention chemical modification of any nucleic acid molecules. Hammond teaches only long dsRNA constructs and not short interfering RNA molecules, and accordingly fails to teach or suggest items a., b., c., d., e., and f. of instant claim 36, items a., b., c., d., e., and f. of instant claim 73, or items a., b., c., d., e., and f. of instant claim 74. Simply stated, Hammond does not teach or suggest **any** limitation of claims 36, 73 and/or 74.

The Examiner also previously cited Cook for its alleged teaching of oligonucleotides comprising glyceryl and various other conjugates and molecules that can be incorporated into oligonucleotides to increase the molecule's pharmokinetics. (Office Action dated December 19, 2005). Other than a statement that "Tuschl et al., Parrish et al., and Cook et al. provide motivation to incorporate chemical modifications into a dsRNA because the modifications are important for mediating RNA interference and important for the molecules (sic) stability", that Office Action contains little if any discussion as to why those skilled in the art would find the reason to combine this with

the other cited references, and as to how this reference, alone and in combination with the other references (assuming they can be properly combined), would give a skilled artisan the reason to not only modify a double stranded nucleic acid molecule, but also to do so in the specific modification patterns as claimed.

Applicants submit that Cook et al. do not even contemplate dsRNA or siRNA, thus Cook provides no motivation whatsoever to incorporate glyceryl molecules into siRNA. Furthermore, the teaching of Cook et al is limited to methods of making oligonucleotide libraries. Thus, Cook et al makes no mention whatsoever of targeting any gene, much less ECGF1 gene. Moreover, Cook fails to contemplate an oligonucleotide having any of the chemical modifications recited in claims 36, 73, and/or 74. Considering that Cook et al fails to teach or suggest siRNA, fails to suggest targeting ECGF1, and fails to teach any of the recited chemical modifications of the instantly claimed nucleic acid molecules, it is difficult to see the relevance of this reference. Cook fails to teach or suggest items a., b., c., d., e., and f. of instant claim 36, items a., b., c., d., e., and f. of instant claim 73, or items a., b., c., d., e., and f. of instant claim 74.. Like Hammond, Cook does not teach or suggest **any** limitation of claims 36, 73, and/or 74.

The cited references are thus entirely silent as to which specific chemical modifications can be made to a double stranded nucleic acid molecule that is 18 to 27 nucleoties long in each strand without compromising the RNA interference activity of those molecules. Applicants submit that more than hundreds of thousands of possible chemical modification patterns can be made to a double-stranded nucleic acid molecule of that size. Therefore, even assuming that those skilled in the art would find the reason to apply chemical modifications used in ribozyme and antisense molecules to double stranded nucleic acid molecules, those cited references, alone or in combination, fail to point out how to narrow the large number of possible chemical modification patterns down to a few. Because "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound **in a particular manner** to establish prima facie obviousness of a new claimed compound," (*Takeda,* at *10) (*emphasis added*), and because here none of the

cited references fails to identify which particular manner of chemical modifications would be suitable, the claims herein are not *prima facie* obviousness.

Moreover, those skilled in the art could not predict what effect chemical modifications would have on double stranded nucleic acid molecules at the time of the present invention even if they had contemplated such modifications. Indeed, the cited Tuschl reference not only teaches away from certain specific modifications, but also suggests the unpredictability of how each modified molecule may fare, because it is clear that some modifications that have been effectively applied on single-stranded nucleic acid molecules can be applied to siRNA molecules but not at each and every level, while others, such as 2'-O-methyl modifications, cannot, at any level.

The Office appears to suggest that a skilled artisan might find the motivation to make the claimed molecules from the cited references because Wyatt teaches that ECGF1 gene plays a role in angiogenesis and is worth investigating through various means of manipulating its expression at the genetic level due to its potential involvement in pathological processes, such as cancer. Applicants respectfully but strongly traverse because the Office's contention boils down to a notion that those skilled in the art can be motivated solely because a gene is known to be associated with certain ailment and thus is an investigation-worthy target.

The knowledge of a worthy target has never been legally sufficient to provide such an expectation. Indeed, such knowledge merely indicates to those skilled in the art a need to investigate the target, but "[r]ecognition of a need does not render obvious the achievement that meets that need." *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.,* 381 F.3d 1371, 1377 (Fed. Cir. 2004). When it comes to modifying what is known in the art, the "mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability" of that specific modification. *See In re Gordon,* 733 F.2d 900, 902 (Fed. Cir. 1984). In other words, the key is the "expectation of success," and without teaching or suggestion of the specific approaches that should be undertaken to achieve inhibition of that target, there can be no reasonable expectation of success. Otherwise the identification of a target without more

may render all subsequently discovered therapeutic agents (chemical or biological) obvious.

Applicants respectfully submit that the Examiner has not satisfactorily explained why it would be within the purview those ordinarily skilled in the art at the time of the present invention to find not only the reason to modify short dsRNA molecules but also modify them in the manner as claimed. The Tuschl article cited by the Examiner actually indicates the mindset of those skilled persons at the time, as evidenced by numerous research publications that came soon thereafter. Those publications uniformly suggest that skilled artisans followed the teachings of Tuschl, and designed siRNAs without any modifications other than the 2-deoxythymidine nucleotides at the 3'-end of the siRNA. *See, e.g.,* Bitko *et al.*, 2001, BMC Microbiology, 1 (34), page 9, left column, "Materials and Methods;" Kuman *et al.,* 2002, Malarial Journal, 1(5), page 9, right column, "Transfection by Inhibitory dsRNA;" and Holen *et al.,* 2002, Nucleic Acid Research, 30, pages 1757-66, Figures 1, 2, and 6. Accordingly, those skilled persons were **in fact** led down a directly opposite path from the one that was taken by Applicants.

For the reasons set forth above, Wyatt *et al.* (U.S. Patent No. 6,716,975), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Tuschl *et al.* (WO 02/44321), Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), and Cook *et al.* (U.S. Patent No. 5, 587,471), alone or in combination, do not render obvious the presently claimed invention. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejections in view of these references.

The Office has maintained the 35 U.S.C. § 103(a) rejection of claims 36, 38, 48-59, and 68-69 as allegedly being unpatentable over Wyatt *et al.* (U.S. Patent No. 6,716,975), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Tuschl *et al.* (WO 02/44321), and Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), in further view of Matulic-Adamic (U.S. Patent No. 5,998,203) and Thompson *et al.* (Nucleic Acids Research 1993). Claims 48-50 have been canceled, rendering the rejection moot as to those claims. Applicants respectfully traverse the rejection with respect to claims 36, 38, 51-59, and 68-69.

The Office Action alleges that Matulic-Adamic teaches double stranded structures comprising abasic terminal cap moieties that provide resistance to degradation and also teaches a double stranded structure comprising separate sense and antisense strands wherein the structure comprises a connecting loop comprising a linker or non-nucleotide linker. The Office Action alleges that Thompson teaches a similar structure and further teaches that linkers increase the efficiency of production and enhance stability of the molecule. The Office Action concludes, based on the cited references, that it would have been obvious to one of ordinary skill to make a dsRNA that is 21 nucleotides in length with chemical modifications targeted to a EDGF1 gene as taught by the combined teachings of Wyatt, Tuschl and Parrish and it further would have been obvious to make a dsRNA where the sense and antisense strands are connected by a linker as taught by Matulic Adamic *et al.* and Thompson *et al.*

First, for the reasons stated above, Wyatt, Hammond, Tuschl and Parrish do not teach the presently claimed siRNA molecules. These reasoning apply with equal force to the Matulic-Adamic and Thompson references. Specifically, the Matulic-Adamic *et al.* and Thompson *et al*. references fail to cure the deficiencies of Wyatt, Tuschl and Parrish. Although Matulic Adamic *et al.* and Thompson *et al.* teach in general terms sugar modifications and teach generally the use of linkers as applied to ribozyme molecules, neither Matulic Adamic *et al.* nor Thompson *et al.* teach or suggest the incorporation of 2'-O-methyl or 2'-deoxy-2'-fluoro modification at one or more nucleotides in siRNA molecules.

Furthermore, the teachings of Matulic-Adamic and Thompson are limited to ribozymes, which are known to be substantially single-stranded and which require at least one stem-loop structure for activity, and do not in any way suggest applying its teachings to double-stranded nucleic acid molecules as are presently claimed. Indeed, at the time of Matulic-Adamic and Thompson, siRNA and RNA interference technology were not known. Thus, neither Matulic-Adamic nor Thompson contemplate siRNA or RNA interference, and certainly do not contemplate chemical modification of siRNA, much less the chemical modifications recited in claim 36, 73, and/or 74.

Specifically, Matulic-Adamic is limited to a teaching of terminal caps in ribozymes. Accordingly, Matulic-Adamic does not, alone or in combination with the other cited references, teach or suggest a chemically modified nucleic acid molecule comprising a sense and a separate sense strand, each stand being independently 18 to 27 nucleotides in length, and each strand comprising the specific pattern of complementarity to a particular ECGF1 RNA sequence, with a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand, with one or more 2'-O-methyl nucleotides present in the sense and antisense strands, and with one to ten 2'-deoxy-2'-fluoro pyrimidine nucleotides present in the sense and antisense strands, as recited in instant claims 36, 73, and/or 74. Simply stated, Matulic-Adamic does not teach or suggest **any** limitation of claims 36, 73, and/or 74.

Thompson merely teaches the use of linkers in ribozymes. Thus, like Matulic-Adamic, Thompson fails to teach or suggest a chemically modified nucleic acid molecule comprising a sense and a separate antisense strand, each stand being independently 18 to 27 nucleotides in length, and each strand comprising the specific pattern of complementarity to a particular ECGF1 RNA sequence, with a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand, with one or more 2'-O-methyl nucleotides present in the sense and antisense strands, and with one to ten 2'-deoxy-2'-fluoro pyrimidine nucleotides present in the sense and antisense strands, as recited in instant claims 36, 73 and/or 74. Thus, like Matulic-Adamic, Thompson does not teach or suggest **any** limitation of claims 36, 73, and/or 74.

The Office Action argues that because ribozymes and siRNA are both nucleic acid molecules, one skilled in the art would have been motivated (presumably with a reasonable expectation of success) based on Matulic-Adamic to incorporate terminal cap moieties to provide resistance and degradation and would have been motivated by Thompson to connect sense and antisense strands via a linker to increase the stability and efficiency of production of siRNA because each of these modifications were known in the art to benefit nucleic acid technologies. (Office Action, page 13). Thus, the Office suggests that because incorporating chemical modifications in nucleic acid inhibitors,

such as antisense and ribozymes, was known to be beneficial in increasing the stability and potency of nucleic acid inhibitors, those skilled in the art would have found the reason to modify double stranded nucleic acid molecules in the same manner.

Applicants disagree on several fronts. First, the mere knowledge that chemical modifications can be made to nucleic acids does not render the specific modifications obvious unless the prior art references specifically suggested the making of those particular modifications. *See In re Gorden,* 733 F.2d 900, 902 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of **the modification**.") *(emphasis added); accord In re Laskowski,* 871 F.2d 115, 117 (Fed. Cir. 1989); *In re Fritch,* 972 F.2d 1260, 1266 (Fed. Cir. 1992); see also *In re Mills,* 916 F.2d 680, 682 (Fed. Cir. 1990); *Ex parte Levengood,* 28 U.S.P.Q. 2d 1300, 1302 (Bd. Pat. App. & Int. 1993). As analyzed above, the recent case, *Takeda,* reaffirms this principle, holding that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a **particular** manner to establish prima facie obviousness of a new claimed compound." *Takeda,* at *10. Therefore, it is improper for the Office to base its obviousness rejection on the mere fact that chemical modifications can be made to nucleic acid inhibitors.

Furthermore, even assuming that teachings of chemical modification in the ribozyme art and/or antisense art can be indiscriminantly applied to modifying other nucleic acid molecules, a notion to which Applicants have traversed above, none of Tuschl, Parrish, Matulic-Adamic, or Thompson teaches or suggests the specific chemical modification patterns recited in the instant claims. Whether or not certain experiments can be performed to obtain the claimed invention is not the standard for obviousness. Rather, those skilled in the art must be motivated to perform such experiments based on the teachings of the prior art. Specifically, in evaluating obviousness, one must look to see if "the prior art would have suggested to one of ordinary skill in the art that **this process** should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art." *In re Dow Chem. Co.,* 837 F.2d 469, 473 (Fed. Cir. 1988)

(emphasis added). Reasonable expectation of success can be found "[w]hen there is a design need or market pressure to solve a problem and there are **a finite number** of **identified, predictable** solutions." *See KSR,* at 1732 (*emphasis added*). On the other hand, reasonable expectation of success is not found when, "[r]ather than identify predictable solutions for [a certain problem], the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *See Takeda*, at *15.

Here, the facts and circumstances are strikingly similar to those of *Takeda.* Even assuming that the chemical modification allegedly taught by Matulic-Adamic and Thompson can be applied to the siRNA art, a contention to which Applicants have traversed above, such experiments would have resulted in hundreds of thousands, if not more, possible chemical modification patterns in a oligonucleotide that is 18 to 27 nucleotides in length. There is nothing in the cited references to teach how to narrow the large number of modified molecules to the claimed ones, and the Office does not so allege. Accordingly, just like the prior art reference of *Takeda* disclosing hundreds of millions of lead compounds and exemplified fifty four compounds, the cited references do not provide the necessary teaching or suggestion that would point those skilled in the art to those claimed molecules.

Further buttressing Applicants' submissions is the fact that, just like in *Takeda*, the closest prior art, which incidentally does not overlap with the references cited herein by the Office, teaches away from making the specific modifications as recited in the instant claims. Specifically, in the time period of about 2000-2001, the high potency of siRNAs and the relative stability of the double stranded structure (as compared to antisense and ribozymes) tended to suggest that **no** additional chemical modification of the molecules would be necessary. It was common knowledge to those skilled in the art at the time of the invention that single stranded RNA and DNA is much more susceptible to nuclease attack than double stranded nucleic acids. Thus, it was thought the relatively unstructured antisense and ribozyme nucleic acid molecules would be expected to require additional stabilization while the substantially double-stranded siRNA molecules would not. An example of this thinking is seen in Elbashir I (EMBO Journal, **20**:6877-6888

(2001)) and Tuschl (U.S. Publ. No. 2002/0086356), where an emphasis was placed on modifying the 3' single stranded ends of the siRNA, with little effort made to modify the double stranded 5' ends. *See, e.g.,* Elbashir I at p. 6881, "*2'-deoxy- and 2'-O-methyl-modified siRNA duplexes*;" and p. 6884, "*Sequence effects and 2'-deoxy substitutions in the 3' overhang*." The methods paper of Elbashir II (Methods **26**:199-213 (2002)) also exemplifies the mindset those of skill around the time of the invention, in that additional chemical modifications are unnecessary for effective RNAi activity.

Applicants further submit that the underlying premise of the Office's argument is the unsubstantiated assumption that all nucleic acid technology is essentially the same and interchangeable. The fatal flaw of such a premise is, however, the lack of evidence suggesting that those skilled in the art held the same view.

In fact, those skilled in the art most certainly did not hold the same view as the Examiner in this respect at the time of the present invention. While little was known about siRNAs, ribozymes were known to have entirely different structural and functional features. Specifically, ribozymes were known to be substantially single-stranded prior to interacting with their targets, in contrast with siRNAs, which are almost entirely in duplex form. It was known at the time that single-stranded nucleic acid molecules are more susceptible to nuclease attack than are their double-stranded counterparts. It was further known that ribozymes would tolerate substantial 5'- and 3'- terminal modifications, whereas the activity of siRNAs is abolished or nearly abolished as a result of blocking the 5'-terminus. Additionally, it was known that the activity of antisense oligonucleotides is destroyed by modifications that alter the DNA-like structure at the core of the molecule, and the activity of ribozymes depends heavily upon the formation of a complex RNA secondary structure requiring at least one stem loop structure for activity. These differences, plus the fact that antisense oligonucleotides and ribozymes function in the nucleus, but RNAi activity occurs in the cytoplasm, would certainly have convinced those skilled in the art that, to suppress gene expression *via* RNA interference, siRNA molecules must take on distinct chemical structures from those of antisense oligonocleotides and ribozymes. Therefore, Applicants submit that the knowledge in the

art in this regard goes to the heart of whether those skilled in the art would believe or be able to predict that the end-cap modifications recited in the present claims, alone or together with the 2'-deoxy-2'-fluoro and/or 2'-O-methyl modifications, would have affected the activities of the siRNA molecules.

Thus, although ribozyme technology is a nucleic acid based technology, it differs substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. Applicants submit that, due to the numerous differences, neither antisense technology nor ribozyme technology provides sufficient insight or guidance into chemical modification of the dsRNAs described by Parrish or Tuschl and therefore one skilled in the art would not have a reasonable expectation of success in making the instantly claimed chemically modified double stranded nucleic acid molecules.

For the reasons set forth above, Wyatt *et al.*, Hammond *et al.*, Tuschl *et al.*, and Parrish *et al.*, in further view of Matulic-Adamic *et al.* and Thompson *et al.* do not render obvious the presently claimed invention. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these references.

The Office has maintained the 35 U.S.C. 103(a) rejection of claims 36, 38, 51-53, 56-59, and 68-69 as allegedly being unpatentable over Meacci *et al.* (Biochem 2002), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Tuschl *et al.* (WO 02/44321), Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), and Cook *et al.* (U.S. Patent No. 5,587,471). Applicants respectfully traverse the rejections.

The Office alleges that Meacci et al. teach a nucleic acid molecule targeted to EDG1 that comprises modified deoxyribonucleotides wherein the nucleic acid molecule is 21 nucleotides in length. The Office expressly states that Meacci et al. do not teach a double-stranded nucleic acid molecule targeted to EDG1 and further do not teach modified nucleotides comprising 2'-deoxy or 2'deoxy-2'fluoro nucleotides or comprise two separate strands connected via a linker molecule. The Office concludes that it would have been obvious to one of ordinary skill in the art to make a dsRNA targeted to EDG1

gene, as taught by Meacci et al. and further it would have been obvious for one of ordinary skill in the art to make a dsRNA which are 21 nucleotides in length with chemical modifications, as taught by Tuschl et al. Parrish et al., and Cook et al. (Office Action dated December 19, 2005 and Office Action dated March 2, 2007 at page 14).

First, for the reasons stated above, Tuschl, Parrish, Hammond, and Cook do not teach or suggest the presently claimed siRNA molecules. Specifically, the present claims require the siRNA molecule targeted to ECGF1 to contain a terminal cap moiety and at least one 2'-O-methyl and 2'-deoxy-2'-fluoro nucleotide on the sense and antisense strands. For the previously stated reasons, Tuschl, Parrish, and Cook, alone or in combination, fail to teach or suggest such modifications as applied to siRNA molecules with a reasonable expectation of success.

The Meacci *et al.* reference fails to cure the deficiencies of Tuschl, Parrish, Hammond, and Cook. Meacci *et al.* merely describe antisense oligonucleotides targeting EDG1. The Office admits that Meacci et al. do not teach a double-stranded nucleic acid molecule targeted to EDG1 and further do not teach modified nucleotides comprising 2'deoxy-2'fluoro nucleotides as required by the present claims. Thus, Meacci et al. fails to teach or suggest a chemically modified nucleic acid molecule comprising a sense and a separate antisense strand, each stand being independently 18 to 27 nucleotides in length, and each strand comprising the specific pattern of complementarity to a particular ECGF1 RNA sequence, with a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand, with one or more 2'-O-methyl nucleotides present in the sense and antisense strands, and with one to ten 2'-deoxy-2'-fluoro pyrimidine nucleotides present in the sense and antisense strands, as recited in instant claim 1. Accordingly, Meacci et al. does not teach or suggest **any** limitation of claims 36, 73, and/or 74.

Furthermore, one skilled in the art would not have found the reason to modify a double stranded nucleic acid molecule, and to do so in the specific manner as claimed from the teachings of Meacci. Meacci *et al.* deal exclusively with antisense technology,

and do not even contemplate chemical modification of antisense. Therefore, Meacci does not, alone or in combination with the other cited references, render the instant claims obvious.

For the reasons set forth above, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejections.

Conclusion

In view of the foregoing amendments and remarks, Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

Date: September 4, 2007

By: /Anita J. Terpstra/
Anita J. Terpstra
Reg. No. 47,132